

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: AOKI et al) Examiner: Anish Gupta
Serial Number: 09/490,756) Art Unit: 1653
Filed: January 24, 2000)
For: METHOD FOR TREATING DYSTONIA)
WITH BOTULINUM TOXIN TYPE B) Irvine, California

DECLARATION UNDER 37 C.F.R. SECTION 1.132

I, MITCHELL F. BRIN, declare as follows:

1. I am over the age of twenty one, competent to testify in a court of law, and could and would testify to the matters set forth below before the United States Patent and Trademark Office, if required to do so.

2. I understand that this declaration will be used to assist prosecution of United States patent application serial number 09/490,756, including to assist to overcome a rejection in the November 8, 2000 office action in serial number 09/490,756.

3. I graduated from the University of Pennsylvania in 1975 with a bachelor of arts in biology (Magna Cum Laude and Phi Beta Kappa) and I received an M.D. degree from the Columbia College of Physicians and Surgeons. I completed neurology and fellowship training at the Columbia University Neurological Institute. In 1994, I joined the Mount Sinai Medical Center as an Associate Professor and Director of the Movement Disorders Program.

I was most recently, attending Physician and Associate Professor of Neurology at the Mount Sinai School of Medicine in New York where I also served as Director of Movement Disorders and held the Bachmann-Strauss Endowed Chair in Neurology. I have directed numerous neurological research programs relating to use of a botulinum toxin in the treatment of movement disorders, such as dystonia.

I was one of the first investigators to examine the use of botulinum toxin for the treatment of medical disorders and I pioneered the use of botulinum toxin for the

treatment of dystonias, including blepharospasm and other debilitating neurological disorders. I have designed and conducted double blind studies examining the use of botulinum toxin for numerous conditions, and have conducted a number of multicenter studies for uses of botulinum toxin.

I founded the American Academy of Neurology course on botulinum toxin, and I have organized numerous courses and symposia on botulinum toxin, and has published extensively on this subject.

I hold many appointments and affiliations, including President and Founder of WE MOVE, an international professional and patient educational not-for-profit organization that focuses on movement disorders. I also serve on the board of directors of the Bachmann-Strauss Dystonia and Parkinson Foundations and the Exceptional Parent Foundation. I serve on the review board of the United States Pharmacopeial Convention and the Steering Committee of the World Congress on Disabilities. I am a member of the American Academy of Neurology Section on Movement Disorders and Co-Founder of the Dystonia Study Group.

I also serve on the editorial and peer-review boards of numerous scientific journals and on the steering committee of the World Congress on Disabilities. I am the recipient of many awards including being elected a Fellow to the American Academy of Neurology; recipient of the FDA's Commissioner's Special Citation for my work with neurological movement disorders; and a Distinguished Service and Honor Award from the American Otolaryngology Society.

A partial list of my publications is attached to this declaration as Appendix A.

By training and experience I am an expert in the therapeutic use of the botulinum toxins, including use of botulinum toxin type B to treat dystonia.

4. I am currently employed by Allergan, Inc, the assignee of the above-identified patent application, as Vice President, *Botox*[®]/Neurology. In this capacity, I oversee the *Botox*[®] (botulinum toxin type A purified neurotoxin complex) development portfolio, and direct clinical programs for uses of the botulinum toxins.

5. I am the co-author of Jankovic J, and Brin M., *Therapeutic Uses of Botulinum Toxin*, New Eng J. Med, 1186-1194;1991 (the "Jankovic reference").

6. The Jankovic reference discusses therapeutic uses of *only* type A botulinum toxin. As of the April 25, 1991 date of the Jankovic reference it was completely unknown as to whether or not botulinum toxin type B would have any therapeutic efficacy in human. Indeed, as far as I am aware, the first reported use of type B botulinum toxin in humans did not occur until 1995.

7. Additionally, the Jankovic reference does not state that botulinum type B can be used as an alternative or in place of botulinum type A, although it does speculate on page 1189, that other botulinum toxins, immunologically distinct from the type A toxin, may have some utility to treat patients who have become non-responsive to type A toxin due to a development of antibodies to the type A toxin.

8. In my opinion, prior to December 28, 1993, it would have been foolhardy and dangerous to use botulinum toxin type B to treat patients with dystonia, such as cervical dystonia, in light of the complete lack of clinical experience with the type B toxin as of that date. Certainly, the 1991 Jankovic reference does not teach, suggest, motivate or recommend use of botulinum toxin type B by physicians to treat any dystonic patients.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statements may jeopardize the validity of the above-identified application or any patent issuing therefrom.

Executed this 8 day of February, 2001, at Irvine, California.



Mitchell F. Brin

ATTACHMENT A

PUBLICATIONS OF MITCHELL F BRIN

A. Original, Peer Reviewed Publications

1. ⁱWormser GP, Donath J, Kennish A, Brin MF, Sanders M. Fatal pneumonia. NYS J Med 1981;1088-1089.
2. [†]Brin MF, Fetell MR, Green PHA, Kayden HJ, Hays AP, Behrens MM, Baker H. Blind loop syndrome, vitamin E malabsorption, and spinocerebellar degeneration. Neurology 1985;35:338-342.
3. Bressman S, Fahn S, Eisenberg M, Brin M, Maltese W. Biotin-responsive encephalopathy with myoclonus, ataxia, and seizures. Adv Neurology 1985;43:119-125
4. Lange DJ, Warner C, Brin M, List T, Fahn S, Lovelace RE. Botulinum toxin therapy: distant effects on neuromuscular transmission. Muscle Nerve 1985;8:624-625.
5. Blitzler A, Lovelace RE, Brin MF, Fahn S, Fink ME. Electromyographic findings in focal laryngeal dystonia (spastic dysphonia). Ann Oto, Rhino, and Laryngoscope 1985; 94:591-594.
6. [†] Brin MF, Pedley TA, Lovelace RE, Emerson RG, Gouras P, MacKay C, Kayden HJ, Levy J, Baker H. Electrophysiological features of abetalipoproteinemia: functional consequences of vitamin E deficiency. Neurology 1986; 36:669-673.
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9. Blitzler A, Brin MF, Fahn S, Lange D, Lovelace RE. Botulinum toxin for the treatment of spastic dysphonia. Laryngoscope 1986;96:1300-1301.
10. Lange DJ, Brin M, Warner C, Fahn S, Lovelace RE. Distant effects of local

injections of botulinum toxin. *Muscle Nerve* 1987;10:552-555.

11. † Brin MF, Fahn S, Moskowitz CB, Blitzer A, Friedman A, Shale HM, Greene PE, List T, Lange D, Lovelace RE, McMahon D. Localized injections of botulinum toxin for the treatment of focal dystonia and hemifacial spasm. *Movement Disorders* 1987;2:237-254.
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13. Blitzer AB, Brin MF, Fahn S, Lovelace RE. Localized injections of botulinum toxin for the treatment of focal laryngeal dystonia (spastic dysphonia). *Laryngoscope* 1988;98:193-197.
14. Blitzer AB, Brin MF, Fahn S, Lovelace RE. Clinical and laboratory characteristics of laryngeal dystonia: A study of 110 cases. *Laryngoscope* 1988; 98:636-640.
15. Vatassery GT, Brin MF, Fahn S, Kayden HJ, Traber MG. Effect of high doses of dietary vitamin E on concentrations of vitamin E in several brain regions, plasma, liver and adipose tissue. *J Neurochem* 1988;51:621-623.
16. Kaplan JG, Pack MD, Horoupian D, DeSouza T, Brin MF, Schaumburg H. Distal axonopathy associated with chronic gluten enteropathy: A treatable disorder. *Neurology* 1988;38:642-645.
17. Younger DS, Chou S, Hays AP, Lange DJ, Emerson R, Brin MF, Thompson H, Rowland, LP. Primary lateral sclerosis: A clinical diagnosis re-emerges. *Arch Neurol* 1988;45:1304-7.
18. Blitzer A, Brin MF, Fahn S. Botulinum toxin injection for the treatment of oromandibular dystonia. *Ann Oto Rhino Laryngol* 1989;98:93-97.
19. † Brin MF, Blitzer A, Fahn S, Gould W, Lovelace RE. Adductor laryngeal dystonia (spastic dysphonia): Treatment with local injections of botulinum toxin (BOTOX). *Movement Disorders* 1989;4:287-296.
20. Ozelius L, Kramer PL, Moskowitz CB, Kwaitkowski J, Brin MF, Bressman SB, Schuback DE, Falk CT, Risch N, de Leon D, Burke RE, Haines J, Gusella JF, Fahn S, Breakefield XO. Human gene for torsion dystonia located on chromosome 9q32-q34. *Neuron* 1989;2:1427-1434.
21. Bressman SB, de Leon D, Brin MF, Risch N, Burke RE, Greene PE, Shale H, Fahn S. Idiopathic dystonia among Ashkenazi Jews: Evidence for autosomal dominant inheritance. *Ann Neurol* 1989;26:612-620.
22. † Brin MF, Fahn S, Loftus S, McMahon D, Flaster E. Relationship between dose of vitamin E administered and blood level. *Ann NY Acad Sci* 1989;570:421-424.

23. Parkinson Study Group. DATATOP: A multi-center controlled clinical trial in early Parkinson's disease, *Archives of Neurology* 1989; 46:1052-1060.
24. Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *New England Journal of Medicine* 1989; 321:1364-1371.
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29. American Academy of Otolaryngology-Head and Neck Surgery. Academy policy statement: Botox for spasmodic dysphonia. *AAO-HNS Bulletin* 1990;9:8.
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32. Blitzer A, Brin MF. Laryngeal dystonia: a series with botulinum toxin therapy. *Ann Oto Rhino Laryngol* 1991; 100:85-89.
33. Lange DJ, Rubin M, Greene PE, Kang UJ, Moskowitz CB, Brin MF, Lovelace RE, Fahn S. Distant effects of locally injected botulinum toxin: A double-blind study of single fiber EMG changes. *Muscle Nerve* 1991;14:672-675.

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50. Bressman SB, Hunt AL, Heiman GA, Brin MF, Burke RE, Fahn S, Trugman JM, de Leon D, Kramer PL, Wilhelmsen KC, Nygaard T. Exclusion of the DYT1 locus in a non-Jewish family with early-onset dystonia. *Mov Disord* 1994;9:626-32
51. *Grillone GA, Blitzer A, Brin MF, Annino DJ, Saint Hilaire MH. Treatment of adductor laryngeal breathing dystonia with botulinum toxin. *Laryngoscope* 1994;104:30-32.
52. *,† Keen M, Blitzer A, Aviv J, Binder W, Prystowsky J, Smith H, Brin MF. Botulinum Toxin for hyperkinetic facial lines: results of a double blind placebo controlled study. *Plast Reconstr Surg* 1994;94:94-99.
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57. *,† Braun N, Abd A, Baer J, Blitzer A, Stewart C, Brin M. Dyspnea in dystonia. A functional evaluation. Chest 1995;107:1309-16.
58. *,† Mezaki T, Kaji R, Kohara N, Fujii H, Katayama M, Shimizu T, Kimura J, Brin MF. Comparison of therapeutic efficacies of type A and F botulinum toxins for blepharospasm: a double-blind, controlled study. Neurology 1995;45:506-8.
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66. *,† Stewart CF, Allen EL, Tureen P, Diamond BE, Blitzer A, Brin MF. Adductor

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*: Publication subsequent to promotion to Associate Professor

†: Brin is primary or senior author

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

English Language Declaration

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF BOTULINUM TOXINS FOR TREATING VARIOUS DISORDERS AND CONDITIONS AND ASSOCIATED PAIN
the specification of which

(check one)

☒ It is attached hereto.

☐ was filed on December 28, 1993 as Application Serial No. 08/173,996 and was amended on

(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119, of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application or which priority is claimed:

Prior Foreign Application(s)

Priority Claimed

_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

_____ (Application Serial No.)	_____ (Filing Date)	_____ (Status) (patented, pending, abandoned)
_____ (Application Serial No.)	_____ (Filing Date)	_____ (Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

Robert J. Baran
Reg. No. 25,806

Walter A. Hackler
Registration No. 27,792

Howard R. Lambert
Reg. No. 27,206

Martin A. Voet
Reg. No. 25,802

Send Correspondence to:
Walter A. Hackler
2372 S.E. Bristol, Suite B
Santa Ana Heights, CA 92707
U.S.A.

Direct Telephone Calls to:
Walter A. Hackler
(714) 851-5010

Full Name of Sole or First Inventor:

K. Roger Aoki

Inventor's Signature:

✓ *K. Roger Aoki*

Date Signed:

✓ 1/4/94

Residence (City, State and/or Country):

25472 Earhart Road, Laguna Hill, CA 92653

Citizenship:

USA

Post Office Address (Street, City, State, Zip Code, Country):

✓

Full Name of Second Joint Inventor (if any):

Michael W. Grayston

Second Inventor's Signature:

✓ *Michael W. Grayston*

Date Signed:

✓ 1/6/94

Residence (City, State and/or Country):

12 Mandarin, Irvine, CA 92714

Citizenship:

USA

Post Office Address (Street, City, State, Zip Code, Country):

✓

Full Name of Third Joint Inventor (if any):

Steven R. Carlson

Third Inventor's Signature:

✓ *Steven R. Carlson*

Date Signed:

✓ 1/8/94

Residence (City, State and/or Country):

29991 Happy Sparrow Lane, Laguna Niguel, CA 92677

Citizenship:

USA

Post Office Address (Street, City, State, Zip Code, Country):

✓

Judith M. Leon

Date Signed:

Fourth Inventor's Signature: Michael M. Leon

✓ 1/20/94

Citizenship:

29992 Running Deer Lane, Laguna Niguel, CA 92677

USA

Post Office Address (Street, City, State, Zip Code, Country):

Fifth Inventor's Signature:

Date Signed:

Residence (City, State and/or Country):

Citizenship:

Post Office Address (Street, City, State, Zip Code, Country):

Full Name of Sixth Joint Inventor (if any):

Sixth Inventor's Signature:

Date Signed:

Residence (City, State and/or Country):

Citizenship:

Post Office Address (Street, City, State, Zip Code, Country):

Full Name of Seventh Joint Inventor (if any):

Seventh Inventor's Signature:

Date Signed:

Residence (City, State and/or Country):

Citizenship:

Post Office Address (Street, City, State, Zip Code, Country):

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	AOKI, <i>et al.</i>) Examiner: (Parent App.: A. Gupta)
)
Serial No.:	Pending) Art Unit: (Parent App.: 1654)
)
Filed:	Submitted herewith)
)
For:	METHOD FOR TREATING)
	DYSTONIA WITH BOTULINUM)
	TOXIN TYPE B) Irvine, California

ASSOCIATE POWER OF ATTORNEY

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Please recognize Stephen Donovan, Reg. No. 33,433, as an Associate Attorney in the above-identified patent application, with full power to prosecute said application, to make alterations and amendments therein, to receive and respond to all communications from the United States Patent & Trademark Office, and to transact all business in the United States Patent & Trademark Office related thereto.

Please direct all correspondence and inquiries to:

Stephen Donovan
Senior Patent Attorney
Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612
Telephone: 714 246 4026
Fax: 714 246 4249

Respectfully submitted,

Date: January 18, 2000

By: Martin A. Voet
Martin A. Voet, Reg. No. 25,208
Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612
Telephone: 714 246 5894

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this Associate Power of Attorney and any additional documents set forth as being enclosed herein are being deposited with the United States Postal Service on the date shown below, with sufficient postage as first class mail in an envelope addressed to Assistant Commissioner for Patents, Washington, DC 20231.

Mary Stickle
Name of person mailing paper

Mary Stickle
Signature of person mailing paper

Date: January 18, 2000

2000-01-18 14:29:00

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PATENT DEPT.

Page 1 of 2

ASSIGNMENT

Docket No. 1949

WHEREAS, WE, K. Roger Aoki, Michael W. Grayston, Steven R. Carlson, and Judith M. Leon, all citizens of the United States of America, residing at 25472 Earhart Road, Laguna Hills, CA 92653; 12 Mandarin, Irvine, CA 92714; 29991 Happy Sparrow Lane, Laguna Niguel, CA 92677, and 29992 Running Deer Lane, Laguna Niguel, CA 92677, respectively, have invented certain new and useful improvements in USE OF BOTULINUM TOXINS FOR TREATING VARIOUS DISORDERS AND CONDITIONS AND ASSOCIATED PAIN for which application for Letters Patent of the United States was filed on December 28, 1993 under application number 08/173,996.

WHEREAS, ALLERGAN, INC., a Delaware Corporation, 2525 Dupont Drive, Irvine, California 92715 is desirous of obtaining the entire right, title and interest in the said improvements and the said application: USE OF BOTULINUM TOXINS FOR TREATING VARIOUS DISORDERS AND CONDITIONS AND ASSOCIATED PAIN

NOW, THEREFORE, in consideration of the sum of One Dollar (\$1.00) to each of us in hand paid, and other good and valuable consideration, the receipt of which is hereby acknowledged, we, the said inventors, do hereby acknowledge that we have sold, assigned, transferred and set over, and by these presents do hereby severally and jointly, sell, assign, transfer and set over, unto the said ALLERGAN, INC.

its successors, legal representatives and assigns, our respective rights, titles and interests, and the entire right, title, and interest throughout the world in, to and under the said improvements, and the said application and all divisions, renewals and continuations thereof, and all Letters Patent of the United States which may be granted thereon and all reissues and extensions thereof, and all rights of priority under International Conventions and applications for Letters Patent which may hereafter be filed for said improvements in any country or countries foreign to the United States, and all Letters Patent which may be granted for said improvements in any country or countries foreign to the United States and all extensions, renewals and reissues thereof; and we hereby authorize and request the Commissioner of Patents of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all Letters Patent for said improvements to the said ALLERGAN, INC.

its successors, legal representatives and assigns, in accordance with the terms of this instrument.

AND WE HEREBY covenant and agree that we will communicate to the said ALLERGAN, INC.

its successors, legal representatives and assigns, any facts known to us respecting said improvements, and testify in any legal proceeding, sign all lawful papers, execute all divisional continuing and reissue applications, make all rightful oaths and generally do everything possible to aid the said ALLERGAN, INC.

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ASSIGNMENT - Page . of 2

APR 18 1994

cket No. 1949

PATENT DEPT.

its successors, legal representatives and assigns, to obtain and enforce proper patent protection for said improvements in all countries.

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 4th day of January, 1994.

State of CALIFORNIA

K. Roger Aoki
ss.: K. Roger Aoki

County of ORANGE

On this 4th day of JANUARY, 1994, before me a Notary Public in and for the State and County aforesaid, personally appeared K. ROGER AOKI known to me to be the person of that name, who signed and sealed the foregoing instrument, and acknowledged the same to be his free act and deed.

SEAL



Mary Lou McNown

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 6th day of JANUARY, 1994.

State of CALIFORNIA

Michael W. Grayston
ss.: Michael W. Grayston

County of ORANGE

On this 6th day of JANUARY, 1994, before me a Notary Public in and for the State and County aforesaid, personally appeared MICHAEL W. GRAYSTON known to me to be the person of that name, who signed and sealed the foregoing instrument, and acknowledged the same to be his free act and deed.

SEAL



Mary Lou McNown

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 18th day of January, 1994.

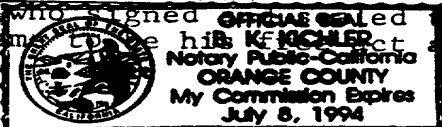
State of CALIFORNIA

Steven R. Carlson
ss.: Steven R. Carlson

County of ORANGE

On this 18th day of January, 1994, before me a Notary Public in and for the State and County aforesaid, personally appeared Steven R. Carlson known to me to be the person of that name, who signed and sealed the foregoing instrument, and acknowledged the same to be his free act and deed.

SEAL



S. R. Carlson

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 20th day of January, 1994.

State of CALIFORNIA

Judith M. Leon
ss.: Judith M. Leon

County of ORANGE

On this 20th day of January, 1994, before me a Notary Public in and for the State and County aforesaid, personally appeared JUDITH M. LEON known to me to be the person of that name, who signed and sealed the foregoing instrument, and acknowledged the same to be his free act and deed.

SEAL



Mary Lou McNown

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REEL

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